29 March 2016
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Capstone

Estimating the Joint Effect of Endocrine Disrupting Chemical Mixtures on Fetal Growth Using Bayesian Hierarchical Linear Regression Modeling: The HOME Study

Abstract

Background: Pregnant women are exposed to endocrine disrupting chemicals (EDCs) through prolonged contact with personal care products, food containers and plastics. Gestational exposure to EDCs may be associated with changes in birth weight and fetal growth, placing children at risk for negative outcomes later in life. **Objective:** To examine the association between gestational exposure to four EDC classes (phthalates, polychlorinated biphenyls (PCBs), polyfluorinated compounds (PFCs) and polybrominated diphenyl ethers (PBDEs)) and infant birth weight. **Methods:** Using data from the Health Outcomes and Measures of Environment (HOME) study, 2003-2006 (n=387), we used Bayesian Hierarchical Linear Regression Modeling (BHLM) to examine the associations between four EDC classes and birth weight. **Results:** Colinearity among the chemical concentrations was severe with correlations as large as 0.98. In BHLM analyses that shrunk the beta coefficients towards the class-specific mean. We found that no individual metabolites from any of the four EDC classes were associated with birth weight. In the BHLM, the parameter μ_β was the average beta coefficient within a chemical class (e.g. phthalates) in relation to birth weight. For a 10-fold increase in chemical concentration, the μ_β values were respectively, 0.89g for phthalates, -1.48g for PCBs, -15.8g for PFCs and -2.14 for PBDEs. In order to put these effect sizes in context, we examined the relative impact of chemical exposure on birth weight versus the effect of poverty on birth weight, based on a Bayesian analysis of four socioeconomic (SES) indicators: low income, low education, no private health insurance, and unemployment. For SES, the estimated value of μ_β was -63.1g. Thus poverty had a larger association with lower birth weight than gestational chemical exposure as measured by a multiplicative factor of x121 for phthalates, x193 for PCBs, x36.1 for PFCs, and x157 for PBDEs. **Conclusion:** Gestational exposure to phthalates, PCBs, PFCs or PBDE had only small associations with differences in birth weight among the HOME study participants. In particular, the average association between gestational EDC exposure and birth weight is approximately 36.1 to 193 times *smaller* than the effect of poverty on birth weight. While no μ_β values attained significance, three were negative. PFCs and phthalates have the greatest associations with birth weight (one negative, one positive). The phthalate and PFC EDC classes, taken within the context of SES, should be considered for closer study.

1. Background

Research studying the effects of environmental contaminants on children has much to contribute to improving child health world-wide (Roundtree, 2012). Research focusing on the impacts of industrial pollutant contamination has led to significant changes improving child health (Roundtree, 2012). One well-known example is the removal of lead from gasoline and paint (Viet et al, 2013; Taylor, Golding, hibbeln & Emond, 2013; Agency for Toxic Substances and Disease Registry (ATSDR), 2007). These, and other, the scientific contributions have been one of the main drivers to successfully creating legislation around limiting the contaminants released into the environment (ATSDR, 2007; United States Senate, 1992; ATSDR, 2014).

One category of chemicals has been an active area of research in regards to child health is the endocrine disrupting chemicals (EDCs) (Braun et al., 2013; deCock et al., 2014). EDCs mimic natural estrogen molecularly and biologically, binding to estrogen receptors (Li et al., 2013). This process can disrupt the endocrine system, which directs the process of fetal growth and development (Braun et al., 2013, de Cock et al., 2014, Stephanidou et al.,2009, Li et al. 2013). In general, infants and children are vulnerable to environmental contaminants due to their immature immunologic and developmental pathways which decrease their capacity to clear contaminants from their bodies (Roundtree, 2012). An especially vulnerable time period for children is while they are in utero (Pereira et al., 2011, Ren et al., 2011, Chapin et al., 2004, Goldman & Shannon, 2011, Bloom et al., 2007) and exposure to EDCs during this time period is thought to potentially impact birth weight, thereby affecting other perinatal outcomes(Buck et al., 2003, Kezios et al., 2012, Murphy et al., 2010).

Efforts to study EDCs and other chemicals, however, have in the past been unable to adequately address one concern: the problem of mixtures (Dominici, Peng, Barr & Bell, 2010; Gennings et al., 2013). The reality of exposure is that infants, children and pregnant women are exposed to a mixture of environmental chemicals, but most of the epidemiological literature only focused on examining one exposure and one outcome (Dominici et al., 2010; Billonet, Sherrill & Annesi-Maesano, 2012). The reason for this is that the statistical methods routinely used at the time were unable to reliably account for the effect multiple inputs, or exposures, on an outcome (Dominici et al., 2010; Gennings et al., 2013). This problem of how to address mixtures is now beginning to be addressed in the literature (Gennings et al., 2013; Billonet et al., 2012; Petit et al., 2012; Braun, Gennings, Hauser & Webster, 2016).

This study aims to examine the effect of low dose exposure to four EDC classes on birth weight, an indicator of child mortality, using anonymized secondary data from the Health Outcomes and Measures of Environment (HOME) study (Braun et al., 2010). The HOME study is a United States-based prospective birth cohort study that examined the effectiveness of lead and injury control measures in the home and the effects of those controls on childhood health outcomes. This study recruited participants from 2003-2006 and collected large amounts of data on low dose exposure to multiple environmental contaminants and multiple measures of early child health (Braun et al., 2010). We use advanced Bayesian statistical methods, specifically Bayesian Hierarchical Linear Regression Modeling, to examine the effect of multiple gestational chemical exposures on birth weight. The four EDC classes

from the HOME study examined in this study were: phthalates, polychlorinated biphenyls (PCBs), polyfluorinated compounds (PFCs) and polybrominated diphenyl ethers (PBDEs).

Phthalates, the first EDC class examined, are used in multiple industries as plasticizers (Serrano et al., 2014). Given the abundance of their production, and thus abundance of human exposure, many studies have examined the potential health effects of elevated phthalate exposure (Braun et al., 2013; Whyatt et al., 2012; de Cock et al., 2014; Lien et al., 2015). The second class under examination in this study are PCBs. PCBs were widely used as industrial coolants until they were largely banned in the 1970's (Lundqvist et al., 2006). PCBs, however, are extremely stable chemically and so take much longer to degrade in the environment, classifying them as a persistent organic pollutant (POP) (Ren et al., 2011). Their 'POP' status has prompted many scientific investigations, as these past exposures can still affect child health (Massart et al., 2005, Jensen et al., 1997, Hertz-Picciotto et al., 2008). The last two classes, PFCs and PBDEs, were widely used as flame retardants and have also been banned in large part (Ryu et al., 2014). PBDEs have also been added to industrial products as water repellants (Ren et al., 2011). Both, however, are still present in the environment and worth investigating as EDCs that possibly affect child health (Lignell et al., 2013, Robledo et al., 2015, Massart et al., 2005). All four EDC classes are present in the environment both as mixtures of specific metabolites belonging to the same class (intra-species mixtures) and as mixtures of different classes (inter-species mixtures). The presence of these mixtures in the environment increases the likelihood that these EDCs have a joint effect in terms of exposure (Billonet et al., 2010). The scientific problem then becomes how to measure these joint effects of EDC mixtures on child health.

There are few statistical methods available that can reliably estimate the joint effects of exposure to a chemical mixture. One method is to simply sum the measurements of the chemical exposures and perform a linear regression with the term that represents the sum of the measurements (MacLehose, Dunson, Herring & Hoppin, 2007; Rauch et al., 2015). This method, however, assumes that all chemicals in the mixture are contributing equally to a joint effect, which may not be the case. It also assumes that all of the components in the mixture act in an additive fashion, which again may not be the case. A different approach is to put all the chemicals together in the same multivariable model. However, if two of the exposures in the mixture are highly correlated, this method runs the risk of producing spurious results due to colinearity (Tu et al., 2005). Other advanced statistical methods for analyzing multiple correlated exposure variables in environmental epidemiology include the weighted quantile sum method (Gennings et al., 2013, Carrico 2013), Principal Component Analysis (Bro and Smilde, 2014) and the environmental risk scores method (Park et al., 2014). However, the differences between these methods are not well understood by stakeholders that use quantitative methods.

Another alternative advanced statistical method is Bayesian Hierarchical analysis (Thomas, Witte & Greenland, 2007; Petit et al., 2011). Bayesian statistics diverge from frequentist statistics (what is normally taught in statistics courses) on the definition of 'probability'. Bayesian statistics states that probability reflects the certainty of a personal degree of belief about an event, in contrast to the frequentist definition, which considers probably to be the frequency of a limited, long running event

(O'Hagan and Luce, 2003). Bayesian statistics assumes that the the unknown parameters in the model come from a *prior distribution which describes available scientific evidence or prevailing beliefs about the parameters*. This assumption allows for the incorporation of decision making into analysis. The prior distribution informs the data and by combining both the prior and the data in the modeling process, inferences can be drawn for that specific population from what is called the posterior distribution.

Bayesian statistics are one of many methods referred to as 'shrinkage' methods because Bayesian statistics compress all of the beta coefficients in a model toward zero (essentially 'shrinking' the data), resulting in generally stable results that avoid the colinearity problem that plagues linear regression and reduces the 'noise' from outlier measurements. A further advantage of 'shrinkage' is that it reduces the rate of false positive results (due to Type I error) because the shrunken beta coefficients are less significant (Gelman, Hill & Yajima, 2012). Other popular examples of shrinkage methods include the LASSO and penalized regression (Cole, Chue & Greenland, 2014).

Hierarchical Bayesian statistics assume that in a linear model described as:

$$Y= \beta_0 +\beta_{x1}*X1+\beta_{x2}*X2 +...\beta_{xn}*Xn +\varepsilon$$

where Y is the dependent variable (birth weight) , β_0 is the y-intercept of the line described by the model, $\beta_{x1}...\beta_{xn}$ are the slope coefficients for each term in the model, X1...Xn are the independent variable terms in the model and ε is the random error in birth weight that is not explained by the model. In a BHLM analysis, the $\beta_{x1}...\beta_{xn}$coefficients are assumed come from a normal distribution that has a mean equal to μ_β and a standard deviation equal to σ_β. This assumption allows for the estimation of μ_β, or the average association between the slopes ($\beta_{x1}...\beta_{xn}$ coefficients) for each term and the dependent variable. This average can then be thought of as a measure of the 'net' or average effect. Thus, a Bayesian Hierarchical Linear Regression Model (BHLM) provides a way to estimate the joint effect of a chemical mixture on an outcome.

Accordingly, the objective of this project was to to examine the effects of gestational exposure to phthalates, PCBs, PFCs and PBDEs on birth weight in the participants of the HOME Study.

2. Methods

2.1 HOME Study

The HOME study is a prospective cohort study based out prenatal clinics in the greater Cincinnati, Ohio metropolitan area. Women were recruited to the study in their first trimester of their pregnancy between 2003 and 2006. Inclusion criteria included living in a home that was built pre-1978, $\leq$19 weeks gestation upon recruitment to the study, intending to continue seeing prenatal care, intending to deliver at one of the collaborating hospitals within the study area, HIV negative and not currently receiving thyroid or seizure medications or undergoing chemotherapy/radiation (Braun et al., 2010). Blood and urine samples were collected at 16 and 28 weeks gestation and analyzed and

quantified (see below for analysis procedures). Birth outcomes including birth weight and duration of gestation (weeks) were obtained from birth records

2.2 Biomarker Analysis and Anthropomorphic Measures

Blood and urine samples were collected at 16 and 28 weeks gestation. For this investigation, nine phthalate monomer metabolites, thirty-five PCB monomer metabolites, five PFC monomer metabolites and eleven PBDE monomer metabolites were investigated. All monomer metabolites were collected in the urine samples and quantified via sensitive and specific isotope dilution or gas chromatography mass spectrometry (Braun et al. 2014).

Monomer metabolites with measurements below the limit of detection (LOD) were assigned a value of LOD/$\sqrt{2}$ (Braun et al., 2014). The phthalate monomer metabolites were normalized with creatinine in units of nanograms per gram creatinine to account for urine dilution. Subsequently, they were $\log_{10}$ transformed to account for skewness in the distribution of the data. Following $\log_{10}$ transformation, if a women gave more than one sample, the phthalate concentrations of the samples were averaged. During all analyses, phthalates were treated as continuous variables. From original data set (n =560), duplicate entries were resolved (n=170) and any entries missing phthalate concentration measurements were eliminated (n=3), for final sample size of n=387. The thirty-five PCB, five PFC and eleven PBDE monomer metabolites were collected via blood serum and quantified using the same method as described above for the phthalates. The PCBs, PFCs and PBDEs were lipid-normalized in units of nanograms per gram serum lipid to account for dilution. Figure 1 illustrates the range of concentrations found for the EDCs under investigation.

2.3 *Confounders*

Potential confounders for the relationship between birth weight and EDC exposure included maternal race, age at delivery, alcohol use, tobacco use as measured by $\log_{10}$-transformed mean blood-serum cotinine concentrations, insurance status, income, IQ score, Beck Depression Index score, marital status, highest level of education achieved, and infant sex. Covariate collection protocols have been described elsewhere (Braun et al., 2014).

Covariates included in the final adjusted models include: maternal race (categorical), age at delivery (continuous), infant sex (categorical), maternal education (categorical), $\log_{10}$-transformed mean cotinine concentration (continuous), maternal income (categorical, <$25,000/year), maternal insurance status (categorical), marital status (categorical) and pre-term birth (categorical, gestational age <37 weeks).

2.4 *Statistical Analyses*

Demographic analyses (Table 1) were conducted using a single-variable linear regression model, with birth weight as the dependent variable and each EDC or potential confounder as the independent variables. Continuous variables were re-coded into categorical variables as necessary using previously

established categories (Braun et al., 2010, Braun et al., 2014). The estimated effect of each metabolite within a class on birth weight was individually examined with single variable linear regression, and then adjusted for the other metabolites within that class and the nine confounders using a multiple linear regression model (Table 2).

Next, each of the four chemical classes was examined with BHLM using the 'rstan' package in R (https://www.r-project.org). Prior to analysis, each chemical class was standardized ($\mu = 0$, $\sigma = 1$). The model specified in this analysis was: $y = \beta_0 + \beta x_1 * X_1 .... \beta_n * X_n$, where y is the outcome (birth weight), β_0 describes the y-intercept, βx_1 - βx_n describes the coefficient associated with each monomer metabolite within a given class, and X_1 - X_n are the exposure variables (the individual metabolite monomers). μ_β, the parameter that estimates the average association between all coefficients in a class and the outcome, σ_β, the parameter that estimates the standard deviation of all the coefficients, and the coefficients specified in the model above (βx_1 - βx_n) were all assigned the following prior distribution: ~N(0,1000). During the modeling, initial sampling was performed with 10,000 sampling iterations to obtain effective sample size (n_eff > 100). In the event that an effective sample size could not be obtained at 10,000 iterations, the sampling was repeated with 20,000 iterations.

2.5 *A sensitivity analysis that compares the effects of EDCs on birth weight with the effect of 4 measures of socioeconomic status on birth weight.*

To give perspective about the size of the effects of EDCs on birth weight, we conducted an additional sensitivity analysis that compares the effects of EDCs on birth weight with the effect of socioeconomic status on birth weight. Four measures of socioeconomic status (SES) were chosen as markers of poverty as an exposure. Using poverty provides a sense of scope within which we can examine the potential effects of the suspected endocrine disrupting chemicals under investigation. These four measures were: reported household income (dichotomized to indicate if income <$25,000), mother's education level (dichotomized to indicate completion of high school/grade 12), employment (dichotomized as yes or no), and insurance type (dichotomized as private or public/none). A BHLM was conducted with these measure to attempt to estimate the average effect of SES on on birth weight.

3. Results

3.1 Demographic Analysis Results

Table 1 describes the unadjusted demographic characteristics of the sample population. The participants in the study were mostly white, married women who held at least a bachelor's degree. Additionally, most were employed upon enrollment in the study, with private insurance coverage and a household income of greater than $25,000 per year. Several maternal demographic characteristics were associated with infant birth weight including: maternal age at delivery, maternal race, maternal marital status, annual household income, type of insurance coverage (private or public/uninsured), maternal education level, maternal IQ, maternal Beck Depression Index (BDI) score, maternal tobacco use and infant sex.

The younger a mother was, the more likely she was to have a child with a lower birth weight. If a mother self-identified as a non-white race, she was more likely to have a child with a lower birth weight. Single mothers also tended to have smaller infants. Mothers who reported a lower annual household income were more likely to have smaller children. If the mother reported having no insurance coverage or being covered through a public insurance plan, she was more likely to give birth to a child with a lower birth weight. Additionally, the less education the mother reported completing, the more likely she was to have a smaller infant. Mothers with lower IQ scores tended to deliver infants with smaller birth weights. Mothers with severe depression are much more likely to deliver smaller infants than women who have minimal, mild or moderate depression. Women who actively smoke tend to have children with lower birth weights, and finally, female infants are statistically more likely to weigh less at birth than male infants.

3.2 Multiple Linear Regression Analysis of Birth weight

Table 2 presents both the results of the Multiple Linear Regression and the BHLM, which will be discussed in a following section. The first column of Table 2 contains the results from the Multiple Linear Regression. Each of the four chemical classes was examined separately and monomer metabolites within a class were controlled for other monomer metabolites within the same class and the nine confounders (maternal race, age at delivery, infant sex, maternal education, log10-transformed mean continine, insurance status, income, marital status and pre-term birth).

Of the nine phthalate monomer metabolites, two, MEP and MEOHP, were statistically significant ($p< 0.05$). In the Multiple Linear Regression model, a ten-fold increase in MEP exposure was associated with a 131g decrease in birth weight. A ten-fold increase in exposure to MEOHP, on the other hand, was associated with a 1137g increase in birth weight. It must be noted, however, when interpreting these results that there is a high amount of correlation between MEOHP and two other phthalate monomer metabolites and this correlation adds unreliability into the estimates provided (see Figure 2a).

None of the thirty-five PCB monomer metabolites were statistically significant. This class exhibited a wide range of estimated associations between the monomer metabolites and birth weight. PCB 153, for example, appears to be associated with a 392 g increase in birth weight for every 10-fold increase in exposure to that PCB monomer. PCB 180, on the other hand, seems to be associated with an 1011 g decrease in birth weight for every 10-fold increase in exposure. As with the phthalates, several PCB metabolites are correlated with each other, which undermines the validity of the estimated associations (see Figure 2b).

Likewise, none of the five PFC monomer metabolites were found to be statistically significant at the 0.05 level. Again, we saw a range of associations between individual monomer metabolites and birth weight. The largest estimated increase in birth weight was in response to a 10-fold increase in exposure to monomer PFNA, with a 122g increase in birth weight. PFOS was the monomer metabolite with the largest estimated decrease, with every 10-fold increase in PFOS exposure associated with a 248g decrease in birth weight.

Lastly, like the PCBs and PFCs, none of the eleven PBDE monomer metabolites were statistically significant and exhibited a range of estimated associations. A 10-fold increase in exposure to the monomer PBDE 100, for example, was associated with a 244g increase in birth weight while a 10-fold increase in exposure to monomer PBDE 66 was associated with a 165g decrease in birth weight.

3.3 Bayesian Hierarchical Linear Model Results

3.3.1 The Effects of Individual EDCs and Birth Weight

The second column of Table 2 contains the results of the BHLM analysis examining the effect of the individual EDCS within each class on birth weight. In this model, the EDCs within each class were adjusted for the other chemicals within their particular class, as well as the eight confounders (maternal race, age at delivery, infant sex, maternal education, log10-transformed mean cotinine level, insurance status, income and marital status).

In contrast to the Multiple Linear Regression analysis results, none of the phthalate monomer metabolites were statistically significant at the 0.05 level. Additionally, the range of estimated associations between each individual monomer metabolite is smaller than the range produced by the Multiple Linear Regression model. Using the BHLM, there is an observed 25g gram increase in birth weight in response to a 10-fold increase in exposure to MEOHP. This is a very different estimate from that seen in the Multiple linear regression, in which the same increase in exposure was associated with a 1137g increase in birth weight. A 10-fold increase in exposure to MEP, using the BHLM, is associated with a 24g decrease in birth weight, which contrasts to the 131g decrease seen in the Multiple Linear Regression. Here we clearly see the 'beta shrinking' and the resulting smaller, but more reliable, estimates.

As with the Multiple Linear Regression, none of the PCB metabolite monomers were significant ($p<0.05$) in the BHLM and like the phthalates, the range of associations in the results of this analysis are smaller. PCB 105 had the largest associated increase in birth weight in relation to an increased exposure. For every 10-fold increase in exposure to PCB 105, there is an associated 6.56 g increase in birth weight. The largest decrease in birth weight seems to be related to PCB 199. For every 10-fold increase in PCB 199 exposure, birth weight appears to decrease by 7g.

None of the PFCs were significant ($p<0.05$) using the BHLM. However, all of the beta coefficients indicate a decrease in birth weight for every 10-fold increase in exposure. Additionally, this class has the narrowest range of beta coefficients compared to the other three classes. PFOS is the greatest in magnitude, with a 10-fold increase in exposure associated with a 26g decrease in birth weight. The smallest in terms of magnitude is PFOA. A 10-fold increase in exposure to PFOA seems to be associated with a 4g decrease in birth weight.

Lastly, none of the PBDE monomer metabolites were significant ($p<0.05$). A narrower range in the BHLM results compared to the Multiple linear regression results was observed. The PBDE monomer associated with the apparent largest gain in birth weight is PBDE 100, with a 10-fold increase in exposure associated with a 9g increase in birth weight. The monomer BB 153, a member of the PBDE class, was associated with the largest decrease in birth weight; for every 10-fold increase in exposure to BB 153, birth weight seems to decrease by 21g.

3.3.2 The Average Effect of an EDC Class on Birth Weight

Each of the EDC classes under investigation contains anywhere from five to thirty-five monomer metabolites. And, as we have seen previously, there exists a wide range of associations between any given monomer metabolites and birth weight. This makes interpreting the results and gaining a broader understanding of the association between any of the four classes and birth weight difficult.

Using BHLM allows for the examination of the average effect of EDC exposure at the class level. In the model, there is a defined parameter called μ_β. This parameter is the estimated average association between the class-specific beta coefficients and birth weight (Table 3). There is also a standard deviation associated with this average estimation, denoted σ_β, and this quantity measures the variability of the effects within the class. The μ_β parameter is a way to attempt to estimate the effect of a group of exposures acting at the same time point; in short, a joint effect, like those seen in a chemical mixture. Table 3 illustrates the estimated association between each of the four chemical classes and birth weight.

A further advantage of reporting μ_β is that it is, in some sense, less vulnerable to publication bias because it prevents the investigator from cherry picking chemicals that are significantly related to birthweight. For example, rather than sorting through 31 PCBs to identify those that are significant, we simply report the average association.

The μ_β value for the phthalate class, for example, is 0.89g. This means that the average association between all nine phthalate monomers and birth weight is an increase of 0.89g. Another way to interpret it is that for every 10-fold increase in exposure to the phthalate class *as a whole,* there is an associated 0.89g increase in birth weight. This increase is not significant at the 0.05 level and the σ_β, 30.3g, indicates that there is a fair amount of heterogeneity around this estimate. It is worth noting that the phthalate class was in the only class to have a positive average association with birth weight; that is, the phthalate class was the only class in which, on average, a 10-fold increase in exposure was associated with increased birth weight.

The μ_β values for the PCB, PFC and PBDE classes also did not attain significance at the 0.05 level. The μ_β values, the average association between the individual monomers as a whole class, for those three classes were, however, associated with decreases in birth weight for every 10-fold increase in exposure. For every 10-fold increase in exposure to PCBs as a class, there was an associated 1.48g decrease in birth weight; a 10-fold increase in exposure to PFCs was associated with a 15.8g decrease in

birth weight and a 10-fold increase in PBDE exposure was associated with a 2.14g decrease in birth weight. As with the phthalate class, the σ_β value of each of these three classes indicates that there is heterogeneity around each of the provided average associations.

3.4 A sensitivity analysis that compares the effects of EDCs on birth weight with the effect of 4 measures of socioeconomic status on birth weight.

In order to provide some context for the joint effect of the EDC classes on birth weight, four measures of low socioeconomic status (SES) were selected from the data for a sensitivity analysis using BHLM (Table 4). The four selected measures were maternal education (dichotomized to indicate whether or not the mother completed high school), insurance status (dichotomized as stated in the methods section), employment (dichotomized as stated in the methods section) and household income (dichotomized to indicate whether or not annual household income was less than $25,000). The BHLM was adjusted for maternal race, age at delivery, infant sex, tobacco use as measured by cotinine concentrations, marital status and if the infant was born pre-term.

Each of the four selected measures of low SES had a significant association with a decrease in birth weight. Of the four measures, having a household income of less than $25,000 per year had the greatest decrease in birth weight of 88.3g. Whether the mother completed high school or not has the second greatest effect in terms of magnitude. If the mother did not complete high school, there is an associated 77.9g decrease in birth weight compared to children whose mothers did complete high school. If the mother reported that she was unemployed at time of intake, that had an associated with a 53.7g decrease in birth weight. Finally, if the mother reported having no insurance or being enrolled in a public insurance program that appeared to decrease her child's birth weight by 20.4g compared to a mother enrolled in a private insurance program.

As with the EDC classes, the quantity μ_β was measured to estimate the average effect of all measures of SES on birth weight. The μ_β did not achieve statistical significance, but indicates that on average, these four measures as a whole decrease a child's birth weight by 63g. There is also a fair amount of heterogeneity around this estimate, as we have seen before with the chemical class estimates ($\sigma_\beta = 116$).

We compared the μ_β value of each of the four EDC classes to the μ_β of the four SES measures. The ratio of the joint effects of each on birth weight, as measured by μ_β, and the difference of the joint effects on birth weight was recorded (Table 4). The ratio of joint effects indicate that the effect of the four selected SES measures on birth weight was greater than the effect of any of the EDC classes on birth weight. Table 4 illustrates that it was 121 times greater than the effect of phthalates, 193 times greater than the effect of PBCs, 36 times greater than the effect of PFCs and 157 times greater than the effect of PBDEs on birth weight.

4. Discussion

Three of the four EDC classes had negative μ_β values. This suggests that the average association between a 10-fold increase to the PCB, PFC and PBDE classes as a whole resulted in a small decrease in birth weight. The greatest decrease in birth weight is associated with exposure to the PFC class; every 10-fold increase in PFC exposure is associated with a 15.8g decrease in birth weight. PFCs also have the lowest SES to EDC class μ_β ratio of 36. The fact that the PFC class has the greatest association with birth weight and simultaneously has the lowest SES to EDC class ratio indications that exposure to this class as a whole may have the greatest impact on birth weight, which corroborates previous studies (de Cock et al., 2014; Apelberg et al., 2007). Two PFC metabolites in this study are associated with a 4.27g and 26.1 g decrease in birth weight for every 10-fold increase in exposure respectively (Table 2). This is consistent with reported decreases in birth weight in previously published studies (Apelberg et al., 2007; Whitworth et al., 2012; Maisonet et al., 2012).

The average association between SES, comprised of four selected measures, and birth weight was larger than the average associations between any of the four EDC classes and birth weight. Having the sensitivity analysis comparing SES to the EDC classes to give a sense of scale provides two advantages. First, it allowed for the identification of an EDC class, the PFCs, that may have a greater impact on birth weight compared to the other three classes. The μ_β value associated with the PFC class was only 36 times smaller than the μ_β value associated with SES (Table 4). This relatively smaller ratio, compared to the other three classes, helps illustrate that the PFCs may have a greater impact on birth weight because it is closer (relatively) to having a similar impact as SES, which appears to have a large impact on birth weight. The SES to class ratio for the phthalate class was 121, which is the smallest out of the three remaining classes (157 for the PBDE class and 193 for the PCB class). This could potentially indicate that phthalates may also have more of an impact on birth weight than the PCB or PBDE classes. It is tempting to think that because a 10-fold increase in phthalate exposure seems to be associated with an increase in birth weight ($\mu_\beta = 0.89$g), that an increase in exposure to this class as a whole may be beneficial, or at the very least is not harmful. It is extremely important to remember, however, that an infant being large at birth carries serious health risks just as the infant being small at birth carries health risks.

The second advantage of having the comparison between the four ED classes and SES is that it serves as an important reminder that exposure to these, and many other, chemical mixtures (approximated in this paper as the four EDC classes) are not occurring in an environmental vacuum. Rather, these exposures are occurring in the context of a socioeconomic environment. By providing the SES to class comparison, we take these results out of an abstract, mathematical setting and place them back in the context in which children and pregnant women are being exposure to these mixtures.

The findings on the associations between each of the four EDC classes and birth weight reported here echo the findings reported in previously published students. The positive, albeit insignificant, association between a 10-fold increase in phthalate exposure and birth weight indicated in this report is

also observed in two other prospective cohort studies, one conducted in France and the other in New York City (Braun et al., 2013). The (insignificant) negative association between increased exposure to PCBs and birth weight was also reported in a study conducted by Robledo et al., (2015). In the Robledo study, the association between increased PCB exposure and decreased birth weight was found to be significant in male infants. Murphy et al. (2010) and a review by Lundqvist et al. (2006) found similar associations between increased PCB exposure and decreased birth weight. Thus, even though the association reported in this study was not statistically significant, it fits in with the larger narrative surrounding PCB exposure and birth weight found in the scientific literature. The negative associations between the PFC and PBDE classes and birth weight is also found in previously published literature (Robledo et al., 2015; Lignell et al. 2015; deCock et al., 2014; Apelberg et al., 2007). There appears to be some debate whether or not a sex effect for PBDE exposure and its impacts on birth weight is present. Robledo et al. (2015) reported that the association between increased PBDE exposure and decreased birth weight was significant in the case of female infants, while Lignell et al. reported the association for both sexes, but noted that the association was stronger in male infants.

There are two main points to keep in mind when interpreting the results of this study. First, the evidence between any given class of EDCs and birth weight is inconsistent. This is more true for the phthalate class than any of the remaining three classes. A literature review by Braun et al. (2013) noted that the number of studies reporting a significant association between increased exposure to phthalates and birth weight and those reporting a null association between phthalate exposure and birth weight are approximately equal in number. There is, however, converging evidence that increased phthalate exposure is associated with the development of childhood respiratory diseases (Braun et al., 2013). Secondly, most of the previously published literature relied on the use of linear regression models and used those models to examine the effects of individual monomer metabolites on birth weight. The results presented here, however, were based on examining the average association between classes of chemicals as a whole and birth weight using a BHLM. Using a BHLM in this paper provided a unique opportunity to move toward a multi-pollutant approach to child environmental health and environmental epidemiology. A multi-pollutant model would more accurately approximate the real world exposure scenario children and pregnant women face and would provide a better basis for legislation and intervention recommendations.

The use of a relatively new modeling method within the context of exploring a perinatal data set is a strength of this study. This model allowed for the examination of a group of chemicals as a group, rather than individually and avoided the colinearity problem. In this paper, however, there were a few limitations. The first is that there are fewer previously published works against which to compare this one. Secondly, the BHLM model used for this paper did not account for interactions between classes. Additionally, there are other possible biases including measurement and recording error in the initial biomarker collection and missing covariate data that resulted in subsequent exclusion that could have potentially resulted in the remaining data being skewed or otherwise not representative.

Gestational age was addressed in this analysis through including pre-term birth, which was defined as birth before 37 weeks gestation. There is debate as to whether or not to include measures of gestational age at all when examining birth weight, because gestational age can act as a variable on the causal pathway between an exposure and birth weight (Wilcox, Weinberg and Basso, 2011). By including and adjusting for measures of gestational age, however, we are able to estimate the effects of EDC exposure on birth weight that may not act through gestational age. There are other methods for adjusting for gestational age, including z-scores (Kark, Tynelius and Rasmussen, 2009) and non-parametric modeling (Zhang et al., 2012), but those are beyond the scope of this analysis.

5. **Conclusion**

We used a Bayesian Hierarchical Linear Regression Model to examine the average associations between gestational exposure to four EDC classes (phthalates, PCBs, PFCs and PBDEs) and birth weight. Our findings indicate that PCBs, PFCs or PBDE have only small or zero associations with differences in birth weight among the HOME study participants. In particular, in a Bayesian analysis of the posterior distribution of μ_β, we found that the magnitude of the associations between 10-fold increases in chemical exposure and birth weight was approximately 36 to 193 times *smaller* than the effect of poverty on birth weight (based on the average of 4 socioeconomic indicator variables). Although none of the EDC classes were associated with changes in birth weight, we observed a small reduction related to exposure to PFCs. The exposure of socioeconomic status is associated with lower birth weight on a much larger scale. These results highlight the need to examine environmental chemicals in the context of their larger environment. This includes remembering that exposures likely occur as mixtures rather than single chemical exposures and that the larger environment includes the socioeconomic environment.

This paper highlighted the advantages of using a statistical modeling method that allows for movement toward a multi-pollutant approach to investigating the effects of environmental chemicals on fetal growth and development. BHLM is one of several methods that may be used to tackle the problem of multiple exposures in the future. Understanding how to best model multiple environmental chemical exposures will provide the best understanding as to how to protect infants and children from these exposures.

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APPENDIX: Tables & Figures

Table 1. Distribution of demographic characteristics among women (n=387) participating in the HOME study, 2003-2006.

	n (%)	**Birth weight (g) mean (SD)**
All participants	387 (100%)	3358 (629)
Age at delivery		
<25	96 (24.8%)	3064 (607)
25-29.9	111 (28.7%)	3466 (892)
30-34.9	118 (30.5%)	3475 (907)
>35	62 (16.0%)	3400 (779)
Race		
White	235 (61.5%)	3513 (594)
Black	121 (31.7%)	3138 (731)
Other	26 (6.8%)	3155 (626)
Marital Status		
Married	246 (64.4%)	3483 (602)
Unmarried, living together	56 (14.7%)	3200 (667)
Unmarried, living alone	80 (20.9%)	3140 (693)
Employment Status		

Unemployed	74 (19.4%)	3279 (619)
Employed	308 (80.6%)	3392 (1406)
Income		
>25,000	124 (32.5%)	3154 (603)
25,000-55,000	92 (24.1%)	3474 (795)
55,000-85,000	98 (25.7%)	3512 (806)
>85,000	68 (17.8%)	3419 (750)
Insurance		
Private	270 (70.7%)	3465 (602)
Public/None	112 (29.3%)	3141 (716)
Education Level		
Bachelor's degree or more	189 (49.5%)	3499 (604)
Some college	98 (25.7%)	3300 (745)
High school	54 (14.1%)	3290 (685)
> High school	41 (10.7%)	3051 (667)
IQ Score		
First tertile (58-101)	108 (32.7%)	3167 (603)
Second tertile (>101-114)	116 (35.2 %)	3383 (869)
Third tertile (115-134)	106 (32.1 %)	3618 (849)
Parity		
Nulliparous	170 (44.2%)	3321 (629)
1 prior pregnancy	186 (48.3%)	3410 (910)
2+ prior pregnancies	29 (7.5%)	3262 (680)
Alcohol Use		
None	216 (56.5%)	3354 (621)
<1 drink/week	114 (29.8%)	3387 (768)
>1 drink/week	22 (5.8%)	3300 (652)
Binge	30 (7.9%)	3442 (663)
Beck Depression Index Score		
Minimal depression (0-13)	299 (80.6%)	3398 (615)
Mild depression (14-19)	45 (12.1%)	3343 (660)
Moderate depression (20-28)	19 (5.1%)	3262 (634)

Severe depression (29-63)	8 (2.2%)	2914 (623)
Tobacco Use (Mean Cotinine Levels)		
Non smoker (<3 ng/ml)	341 (88.1%)	3378 (627)
Active Smoker (>3 ng/ml)	46 (11.9%)	3217 (668)
Gender of Baby		
Male	179 (46.3%)	3466 (622)
Female	208 (53.7%)	3266 (914)

S.D. - Standard deviation

Table 2. Multiple linear regression and Bayesian hierarchical linear regression models (BHLM) for the association between EDCs and birth weight. The first column describes the estimated beta coefficients for from multiple linear regression with birth weight as the dependent variable. The second column describes estimates the beta coefficients for each class from a BHLM that shrinks the coefficients towards a common mean μ_β.

Chemical	**Regression coefficient - Difference in birthweight (g) associated with 10-fold increase in chemical exposure concentration**	
	Multiple linear regression Model**	**Bayesian Hierarchical Linear Model****
Phthalates		
MBP	-15.90	0.05
MIBP	-1.48	0.46
MBZP	-39.3	1.27
MEP	-130.9*	-24.2
MCPP	9.94	-0.24
MECPP	-279	0.66
MEHP	-135	-5.51
MEHHP	-619	10.8
MEOHP	1137*	25.2
PCBs		
PCB 28	66.5	1.39
PCB 44	43.6	-2.75
PCB 49	-60.7	-5.17
PCB 52	-188	-6.52
PCB 66	-111	-2.48
PCB 74	-182	-2.04
PCB 87	130	-0.69
PCB 99	-306	0.68
PCB 101	119	3.43
PCB 105	197	6.56
PCB 110	-7.35	-0.42
PCB 118	13.4	1.66
PCB 128	88.8	2.34
PCB 146	-53.5	-2.28
PCB 149	-270	-4.16
PCB 151	149	0.90

PCB 153	392	-2.15
PCB 156	-3.92	-3.19
PCB 157	-42.6	-3.94
PCB 167	-88.2	-3.44
PCB 170	139	-4.09
PCB 172	45.4	-0.67
PCB 177	80.7	1.34
PCB 178	-27.4	-3.73
PCB 180	-1011	-5.10
PCB 183	108	1.06
PCB 187	169	-1.19
PCB 189	68.1	-0.64
PCB 194	100	-3.52
PCB 195	32.6	-2.04
PCB 199	-146	-7.41
PCB 206	123	0.73
PCB 209	-28.3	-3.13
PCB 138.158	300	1.50
PCB 196.203	-197	-5.95
PFCs		
PFOA	75.5	-4.27
PFOS	-248	-26.1
PFNA	122	-7.69
PFHXS	-71.5	-18.9
PFDEA	-196	-20.3
PBDEs		
BB 153	-99.0	-21.3
PBDE 17	115	1.52
PBDE 28	39.6	9.36
PBDE 47	-130	5.31
PBDE 66	-165	-14.5
PBDE 85	9.68	0.14
PBDE 99	60.3	8.61
PBDE 100	244	9.54
PBDE 153	-163	-14.4
PBDE 154	-59.5	-6.39
PBDE 183	-8.83	-2.88

'*' - statistical significant with p<0.05

'**' - Regression models were adjusted for: maternal race, age, child gender, maternal education, cotinine exposure, income (< $25,000/year), insurance, marital status and pre-term birth (<37 weeks gestation).

Table 3. Bayesian estimates of the average of the beta coefficients, denoted μ_β, for each chemical class on birth weight in the HOME study, 2003-2006, n=387. The first columns gives the estimate of μ_β within each chemical class. The second column gives σ_β which is the standard deviation (heterogeneity) of the beta coefficients within each chemical class. For example in the phthalate class, we have μ_β =0.89. This means that, when averaging across the 9 different phthalates, that a 10-fold increase in phthalate exposure concentration was associated with a mere +0.89gram (non-significant) increase in birth weight.

	Average regression coefficient μ_β(standard deviation σ_β) that describes differences in birthweight (g) associated with 10-fold increase in chemical exposure concentration (95% CI)	
Exposure	**μ_β***	σ_β*
Phthalates	0.89** (-29.6, 27.1)	30.3
PCBs	-1.48** (-7.29,4.29)	11.1
PFCs	-15.8** (-62.6, 32.1)	37.3
PDBEs	-2.14** (-26.4, 19.7)	28.3

** - Not statistically significant from zero, p<0.05.

* Estimates of μ_β, and σ_β from the BHLM were adjusted for: maternal race, age, child gender, education, cotinine exposures, income, insurance status, marital status and pre-term birth.

Table 4. A Bayesian comparison of the relative effect of SES versus EDCs on birth weight. To provide context for the association between EDC exposure and birth weight, four measures of socioeconomic status (SES) were selected from the HOME study (2003-2006, n=387). These measures are described in Table 4a, illustrating their individual associations with birth weight. Additionally, Table 4a shows the average regression coefficient, denoted μ_β for the association between SES and birth weight. In contrast, Table 4b shows the relative effects of SES versus chemical exposure on birth weight.

Table 4a - SES and birthweight		
SES Measures	**Regression coefficient - SES measured and birthweight**	**Average regression coefficient - SES measure and birthweight**
Education (Did not complete high school)	-77.9*	μ_β= -63.1 σ_β = 116
Income (<$25,000)	-88.3*	
Insurance (None or public)	-20.4*	
Unemployment	-53.7*	
Table 4b - What affects birthweight more: SES or chemical exposure?		
Class compared	**Ratio of Effects (95% CI)**	**Difference of Effects (95% CI)**
SES vs Phthalates	121 (0.0009, 115)**	-33.5 (-248, 189)
SES vs PCBs	193 (0.002, 408)**	-25.9 (-600, 412)
SES vs PFCs	36.1 (0.0003, 45.1)**	11.4 (-304, 283)
SES vs PBDEs	157 (0.002,166)**	-1.71 (-311, 252)

* Not significant at p=0.05

** Significant at p=0.05

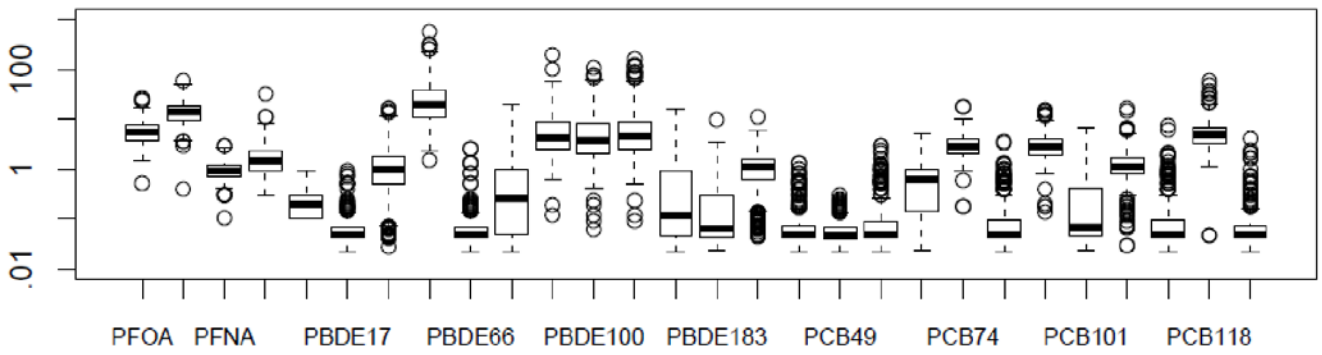
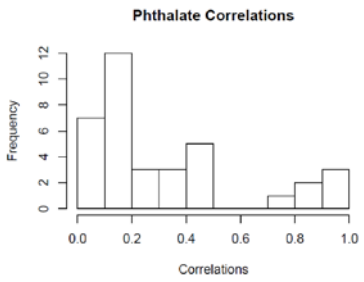
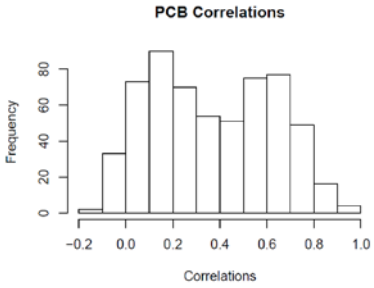


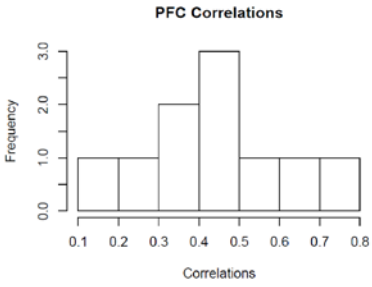
Figure 1. Boxplots of Chemical Class Concentrations. Log10-transformed concentrations of chemicals of interest in this investigation from the HOME Study 2003-2006 cohort, n=387. Concentrations are displayed in units of ng/g lipids (PCBs, PBDEs), µg/g creatinine (phthalates and BPA), and µg/L (PFAS).



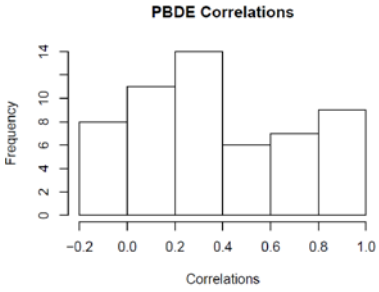
2a. Correlation of Phthalates.



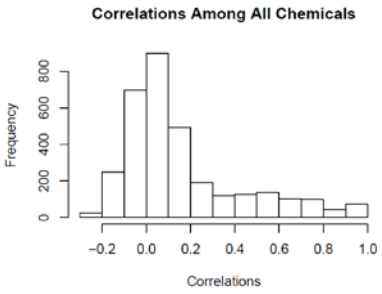
2b. Correlation of PCBs



2c. Correlation of PFCs



2d. Correlation of PBDEs



2e. Correlations among all chemicals in all four classes.

Figure 2. Histogram of correlation of the four chemical classes under examination. The four chemical classes (HOME Study, 2003-2006, n=387) had a range of correlations within the same classes, with some exceeding a correlation coefficient of 0.8. When all four classes were combined together to examine correlation among all the classes, the majority had a correlation coefficient between 0.0 and 0.2.

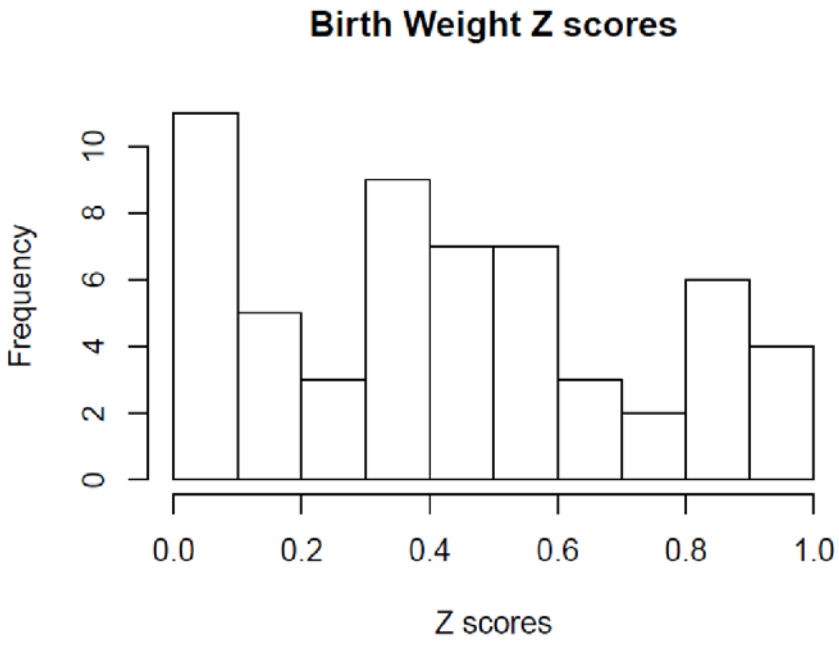


Figure 3. Histogram of z-scores of birth weight (HOME Study, 2003-2006), n=387. The z-scores describe how far away, in terms of standard deviations, the birth weights in this study are from the mean. Overall, the histogram illustrates that the shape of the distribution of birth weights around the mean can be described as asymmetric, with some birth weights being very low. These low birth weights are potentially the weights of pre-term children in the study.

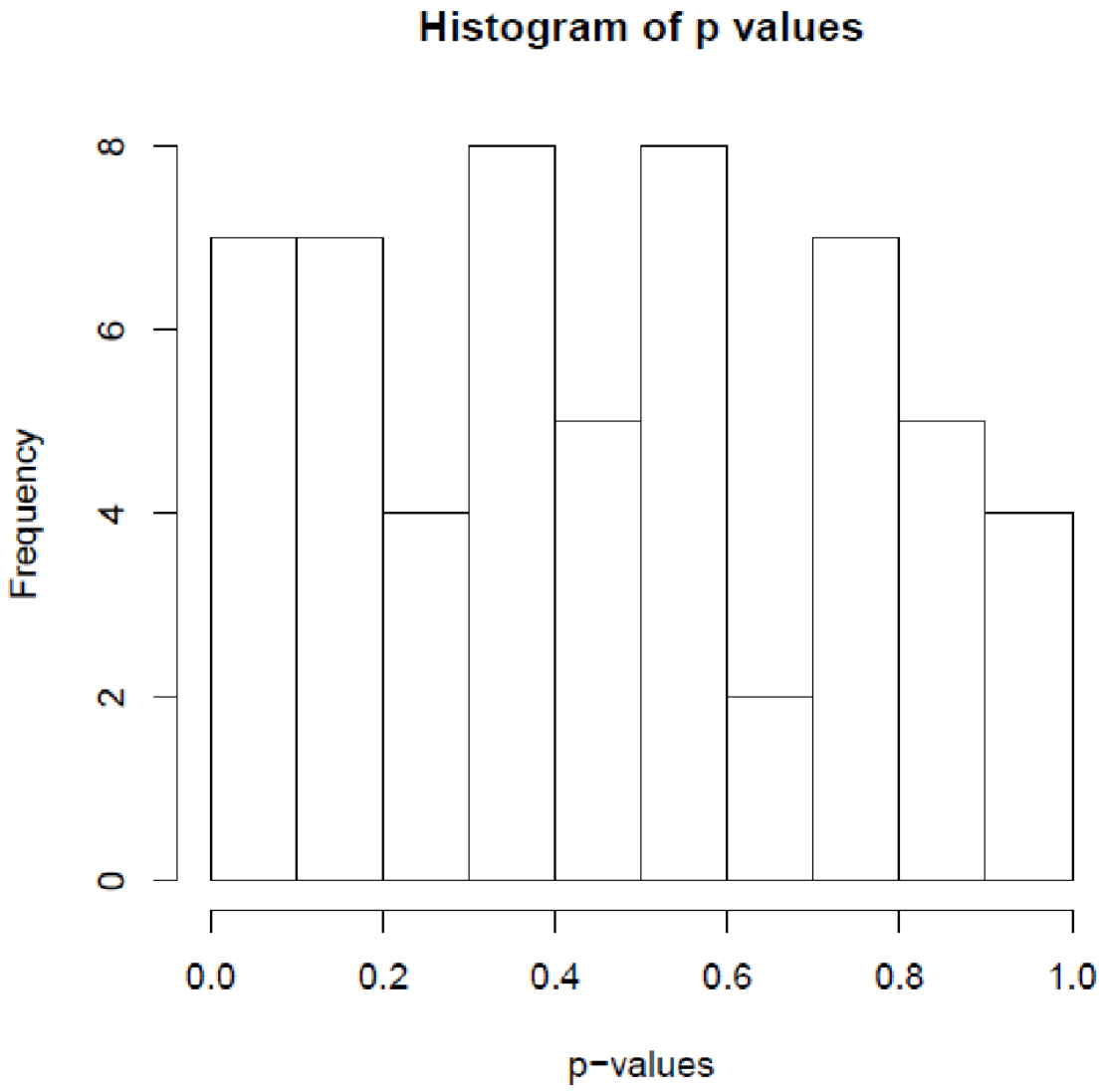


Figure 4. Histogram of p-values (a). The p-values are the results of the single variable linear regression for each individual chemical and birth weight in the HOME Study (2003-2006) data, n=387. The p-values are adjusted for maternal race, age, income, education and infant sex. The vast majority of the p-values are greater than 0.1.

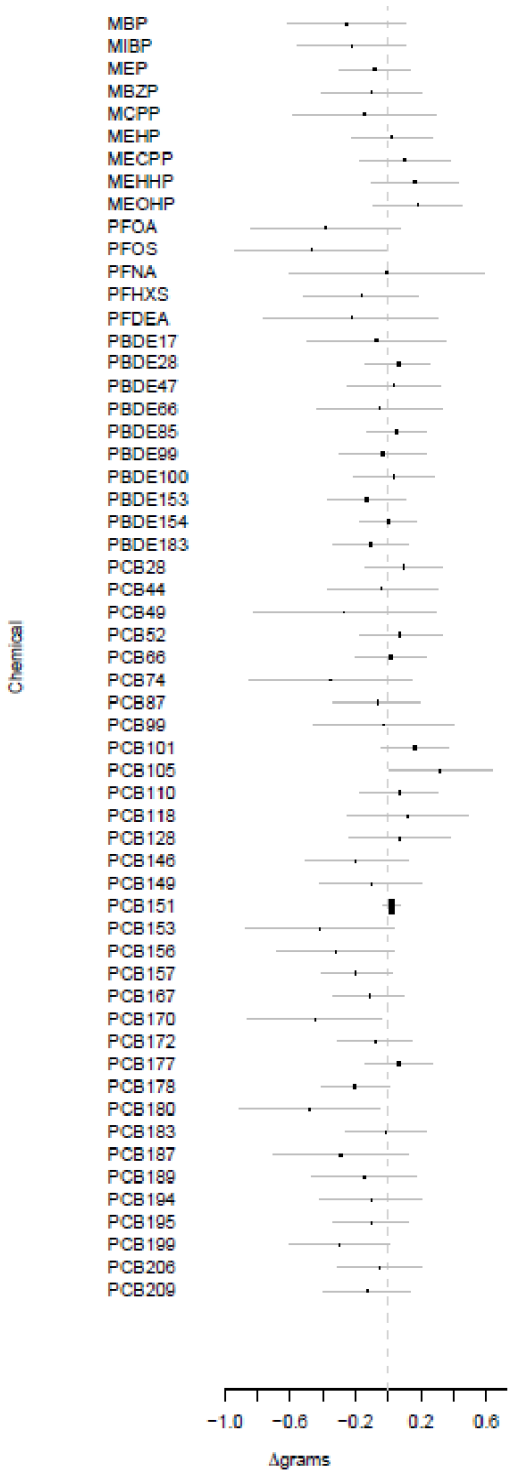


Figure 5. Forrest plot of p-values. This figure describes the regression coefficients for each of the chemicals and birth weight in a single variable multiple linear regression (adjusted for maternal race, age, income, education and infant sex) and the confidence interval associated with that regression

coefficient taken from the HOME Study data (2003-2006, n=387). Many of the regression coefficients are less than zero (to the left), but with confidence intervals that cross zero.